

Polycystic Ovary Syndrome

-diagnosis and treatment

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Abstract:

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder, and a major cause of infertility in women. An excessive amount of androgen hormones are produced by polycystic ovaries in PCOS with irregular menstruation and anovulation as result. The most common early symptoms are infertility, hirsutism and acne. Type 2 diabetes mellitus, metabolic syndrome, and possibly cardiovascular disease and endometrial carcinoma are all associated as lifelong implications with the diagnosis of PCOS. Medical treatment of PCOS should be tailored to the woman's symptoms and goals. In broad terms, treatment includes diet regulation, weight loss, oral contraceptives, clomiphene citrate and in vitro fertilization.

Introduction:

Polycystic ovary syndrome (PCOS) is the most common cause of infertility in women (1). The major clinical features of polycystic ovary syndrome include menstrual dysfunction, anovulation and signs of hyperandrogenism. Women with PCOS often have a normal or slightly delayed onset of menarche, and in some women the irregularities in menstrual cycle develop when they gain weight. The menstrual irregularities that women with PCOS have are characterized by oligo- or amenorrhea with infrequent or absent ovulation leading to infertility (2). The clinical signs of hyperandrogenism are hirsutism with thick facial and/or body hair in a typically male pattern, acne, and in some cases male pattern hair loss.

I first got introduced to this syndrome by a friend of mine who told me about her symptoms and that she was diagnosed with PCOS at the age of 19. Little did I know about this complex syndrome before I sat down and researched about it on the internet the next day. I then realized that being diagnosed with this syndrome would make a huge impact on a young woman's life. Since then, I have been curious to learn more about PCOS. What is PCOS? What are the main criteria to tell ascertain person that she has PCOS? What kind of clinically manifestations will a person with PCOS have? What is the main medical treatment for PCOS?

The aim of this study was to describe PCOS amongst adolescents, in infertile women and in mature women. As the title of this master thesis already has revealed, "Polycystic Ovary Syndrome - diagnosis and treatment" will be the main topics.

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Methods:

The project method is a non-systematic literature review searching the databases UpToDate, PubMed and Cochrane library. The search was limited to original articles and reviews published in English.

The search words were as following:

- pco
- pcos
- pcos AND diagnostic
- pcos AND infertility
- pcos AND treatment

Part I: Polycystic Ovary Syndrome – Overview

The diagnosis of PCOS includes many factors that mould together to make the final diagnosis. There are plenty of different definitions on this syndrome depending on which region in the world you come from, and multiple varying mechanisms that describe the etiology behind PCOS. There are many divergent clinical symptoms and signs of this syndrome. Having a little background information about the definition, epidemiology, etiology, and the clinical presentation of the syndrome, it will help us in diagnosing PCOS. It is also important to differentiate PCOS from PCO. The term PCO or polycystic ovaries refers to the description of the ovaries as seen on the ultrasonography. Having no other symptoms or hormone findings, many women have ovaries that are polycystic (3). On the other hand, PCOS includes PCO and also other signs and symptoms, thus the name "syndrome". It is not fully known if PCO can develop to PCOS (3).

Definition:

Before diagnosing PCOS, it is important to make clear what definition to use for the diagnosis. As it is a complex syndrome, it might have different criteria as well. Stein and Leventhal were the first to describe PCOS, and associated amenorrhea with polycystic ovaries and sign of hirsutism (4). PCOS includes a majority of different features that are not otherwise explained with cutaneous signs of hyperandrogenism (e.g. hirsutism, acne), menstrual irregularity (e.g. oligo- or amenorrhea, or irregular bleeding), polycystic ovaries (one or both), obesity and insulin resistance (4).

An expert conference held in 1990 sponsored by the National Institute of Child Health and Human Disease (NICHD) of the United States National Institutes of Health (NIH) proposed the following criteria for the diagnosis of PCOS (5):

- Oligo ovulation or anovulation manifested by oligomenorrhea or amenorrhea,

- Hyperandrogenism or hyperandrogenemia
- Exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism.

In 2003, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) recommended that at least 2 of the 3 following features are required for PCOS to be diagnosed (6):

- Oligomenorrhea or amenorrhea
- Hyperandrogenism or hyperandrogenemia
- Polycystic ovaries on ultrasonography

In October 2013, the Endocrine Society released practice guidelines for the diagnosis of PCOS (7).

Among their conclusions, was the recommendation of ESHRE criteria for diagnosing PCOS, with the presence of at least two of the following: androgen excess, ovulatory dysfunction or polycystic ovaries.

Epidemiology:

Depending on the definition used, population and period for investigation, 5-8 % of women in fertile age do have PCOS according to some European studies (8). There is, however, a great deal of ethnic variability, especially when it comes to hirsutism and metabolic syndrome. As an example, women from East and Southeast Asia have less hirsutism than Caucasians given the same serum androgen values. In hirsute women, the incidence of acne, menstrual irregularities and polycystic ovaries are significantly increased (9). PCOS affects premenopausal women, and the age of onset is most often perimenarchal. However, in some cases the clinical recognition of the syndrome may be delayed by failure of the patient to become concerned by irregular menses, hirsutism or by the overlap of PCOS findings with normal physiologic maturation during the two years after menarche. There might be a genetic predisposition in women with PCOS, and the syndrome may not be unmasked before they gain

weight (2).

Etiology:

PCOS affected women may have abnormalities in the metabolism of androgens and estrogen, while other affected women are genetic predisposition for the syndrome. It is questionable why the clinical appearances of this syndrome are so different. Being a complex syndrome of uncertain cause, there are many different mechanisms leading to PCOS. First of all, there are irregularities in the metabolism of androgens and in the control of androgen production. These patients may be encountered with high serum concentrations of androgenic hormones, such as testosterone and androstenedione. Nevertheless, a patient may have normal androgen levels, though there is considerable individual variation (10).

Hyperinsulinemia and peripheral insulin resistance are also associated with PCOS. High levels of insulin may augment the gonadotropin levels, thereby affecting the function of the ovaries. Insulin resistance can lead to metabolic and reproductive disorders. There might also be a correlation between hyperinsulinemia and suppression of hepatic generation of sex-hormone-binding-globulin (SHBG), which may increase androgenicity (11). In PCOS patients, hyperinsulinemia is responsible for dyslipidemia and for elevated levels of plasminogen activator inhibitors (PAI-1). Elevated levels of PAI-1 are a risk factor for intravascular thrombosis (11).

A suggested mechanism for high androgen levels and anovulation is that under the increased effect of luteinizing hormone (LH), the ovarian theca cells stimulation is also increased (12). These cells then increase the production of androgens. Because of a decreased FSH ratio to LH, the granulosa cells are not able to aromatase the androgens to estrogens, which can lead to reduced levels of estrogen and anovulation (13).

Polycystic ovaries are formed when hyperandrogenemia, hyperinsulinemia and modified intraovarian paracrine signals together make the follicles go into arrest, causing atresia (10). This in turn causes irregularities in menstrual cycle, subfertility associated with anovulation, and thus follicles having a prolonged survival. As a consequence, an accumulation of small antral follicles will result (10).

Part II: Polycystic Ovary Syndrome – Diagnosis

As mentioned earlier, there are many varieties in the clinical presentation of PCOS. In this section some of the most frequently occurring clinical manifestations are emphasized. The most used diagnostic criteria for PCOS are referred in the table below.

ESHRE criteria 2003
Must include two of the following: <ul style="list-style-type: none">• Anovulation or oligo-ovulation• Clinical or biochemical signs of hyperandrogenism• Polycystic ovaries

Clinical manifestations:

Menstrual disorders: Abnormal menstrual cycle might be the most common symptom (14). History of menstrual disturbance dating back to menarche is often typical amongst patients with PCOS.

Oligomenorrhea occurs in some women, also menstrual bleeding that occurs with intervals of 35 days to 6 months or amenorrhea.

Infertility is another consequence of anovulatory menstrual cycles. Higher rate of abortions amongst PCOS women has been observed, but the causes are not quite known (15).

Hyperandrogenism manifests clinically as excess body hair in a male distribution pattern. Typically, hair is seen on the upper lip, on the chin, around nipples and along linea alba of lower abdomen (16). The Ferriman-Gallwey score grades 11 body areas from 0 (no hair) to 4 (frankly virile), and a total score of 8 or more is considered abnormal for adult Caucasian women (16).

In some patients acne occurs as well. Having seborrheic skin as a PCOS patient, the chances of getting acne as a consequence of oil, bacteria, and dead skin cells getting trapped inside the pores of the skin are higher compared to normal or dry skin. In women with PCOS, androgen levels are often elevated, including dihydrotestosterone. This metabolite promotes oil production, which can lead to the pores getting clogged. Rise in oil production also manifests as greasy hair in patients with PCOS (17). Increased muscle mass, voice deepening and hyperandrogenism are related to more extreme forms of PCOS. As a differential diagnosis, symptoms of hyperandrogenism could also be consistent with androgen producing tumors (15).

Obesity and metabolic syndrome: Up to 80 % of women with PCOS are obese, based on waist circumference (18). Even though a controlled study has not been performed, one single study showed a 43% prevalence of abdominal obesity in women with PCOS, including dyslipidemia, higher blood pressure and hyperinsulinemia (1). Women with PCOS should be assessed for their cardiovascular risk by evaluating their BMI, fasting lipid and lipoprotein levels (10).

Obstructive sleep apnea syndrome (OSAS): Obstructive sleep apnea syndrome has been observed in many women with PCOS, which again is a huge risk factor for cardiovascular diseases (19). Excessive daytime somnolence is an important question that patients should be asked about.

Hormone analyses:

Follicle stimulating hormone (FSH) level should be checked in patients with PCOS. In most cases, FSH levels are within the reference or even low. There are elevated levels of luteinizing hormone (LH), and the LH:FSH ratio is higher than 3 (13).

Measuring total and free testosterone levels are sensitive indicators of androgen excess. Levels of sex-hormone-binding-globulin (SHBG) are usually low in women with PCOS. Elevated levels of androstenedione are also common. Thyroid stimulating hormone (TSH) levels should be evaluated, because thyroid dysfunction can cause amenorrhea and hirsutism.

Imaging:

Gynecologic ultrasonography, especially using a transvaginal probe, is a good screening tool for PCOS patients. Ultrasonography can be used to evaluate the ovarian morphology, specifically looking for small ovarian follicles. Bilateral enlarged ovaries with multiple small follicles are seen on ultrasound. The ovarian size is increased, with 12 or more follicles measuring 2-9 mm and most follicles of similar size. The endometrium may appear thickened, resembling that of a proliferative endometrium. A transrectal approach with ultrasound is an alternative in virginal patients (18).

Serum concentrations of anti-Müllerian hormone (AMH) have been shown as a useful indicator in the diagnosis of PCOS. AMH is usually at least two to three times higher in women with PCOS compared to normal women (15). There is a correlation between the number of small antral follicles seen on transvaginal ultrasonography and serum AMH concentration. A high concentration of AMH is however not a criteria in the diagnosis of PCOS.

If suspecting a tumor, CT or MRI methods for imaging are recommended.

Other laboratory screenings:

The diagnostic approach needs to exclude all other disorders that can result in the same clinical presentations as mentioned above, such as menstrual irregularities and hyperandrogenism. Cushing syndrome, acromegaly, adrenal and ovarian tumors and thyroid dysfunction may be some of the differential diagnosis (18, 19). It is therefore important to make imaging studies and laboratory screenings to rule out other disorders and make a clearer diagnosis.

As a screening for Cushing syndrome, a 24 hour urine sample can be used, looking for urinary free cortisol and creatinine levels that are at least four times the upper limit of normal (20).

Glucose, insulin and lipids: As discussed earlier, the prevalence of glucose tolerance and type 2 diabetes mellitus is higher in women with PCOS, and especially in patients with metabolic syndrome an oral glucose tolerance test should always be taken (21). Patients with PCOS that are pregnant should also be screened for gestational diabetes, because these women do have a higher rate of diabetes than the average population (19). Cholesterol levels should be measured, because in some women with PCOS an abnormal lipid profile is often shown (22). Insulin resistance and inflammatory markers have been shown to be useful in identifying adolescent girls with PCOS who have a higher risk of developing metabolic syndrome (23).

Part III: Polycystic ovary syndrome -Treatment

Being a syndrome, this disorder does involve various different signs and symptoms, and patients do come in different ages, all from adolescents to mature women. Each and every single patient has to be treated independently and distinct from one another. In this part, the treatment of adolescents, treatment of infertile women with desire of having children and the treatment of mature women will be discussed.

Diet and exercise should be considered a first line of treatment for women with PCOS, because you can easily reduce some of the symptoms with such simple steps. These steps include the majority of PCOS patients. Pharmacologic treatments are reserved for women with PCOS that also have signs and symptoms of hirsutism, anovulation and menstrual irregularities.

Weight loss and diet regulation reduce the risk of diabetes. Some studies have shown that this approach has been better than treatment with medications (18). Lifestyle modifications have been beneficial in restoring ovulatory cycles, improved hyperandrogenic features and in achieving pregnancy in women with PCOS.

PCOS patients - adolescents without infertility:

Oral contraceptives to induce regular menses and to increase sex-hormone-binding-globulin (SHBG) production are recommended for long term management of menstrual dysfunction (18). If hirsutism is not enough reduced, adding an androgen-blocking agent has been shown effective.

For patients with PCOS, the oral contraceptive of choice is called Diane. It contains estrogen (ethinylloestradiol) which is the most common estrogen used in nearly all the oral contraceptive pills. What makes Diane unique is the progesterone agent, cyproterone acetate. Cyproterone acetate is an anti-androgen hormone, and it therefore reduces the conversion of testosterone to its more active forms (24). Thereby, it reduces acne and also have a slightly effect on the abnormal hair growth. Potential side effects of Diane include menstrual cycle irregularity, weight gain, breast tenderness, depression and a slightly increased risk of thrombosis compared to other oral contraceptives (24). A thorough family history with no incidents of thrombosis or other coagulopathy, is in most cases enough for giving cyproterone acetate in Norway.

Hirsutism can be reduced with laser treatment or electrolysis. Both reduce the amount of hair over time, but many treatments are required. A laser beam passes through the skin to an individual hair follicle. The intense heat of the laser damages the hair follicle, which inhibits future hair growth (25). In electrolysis, a very fine probe is inserted into the hair follicle, destroying the growth center of the hair with chemical or heat energy. In Norway, there is given refund of facial laser and electrolysis treatment. Short-term, non-pharmacologic treatments of hirsutism, such as shaving, bleaching creams and waxing on other body parts are not included.

PCOS patients with infertility:

Clomiphene citrate: For a patient desiring fertility, ovulation induction can be obtained with clomiphene citrate (18). The mechanisms of clomiphene citrate are not fully known, but being an estrogen receptor antagonist, it does have the properties of interrupting the negative feedback that estrogen normally produces at the level of the pituitary and the hypothalamus. As a result of this, the follicle stimulating hormone production increases and results in follicular growth and maturation (26).

If clomiphene citrate fails, *gonadotropins* or *laparoscopic ovarian surgery* can be used to treat infertility (19, 28) Laparoscopic ovarian drilling is a surgical treatment that can trigger ovulation in women who have PCOS. A laser or diathermy is used to destroy parts of the ovaries. This treatment results in a dramatic lowering of male hormones within days. Many women, who fail to ovulate with clomiphene, will respond when these medications are reintroduced to the system after ovarian drilling.

A Norwegian gynecologist, Halvard Gjønness, made a long-term observational study where he examined late endocrine effects of ovarian electrocautery in women with polycystic ovary syndrome. Ovarian electrocautery was performed through the laparoscope. And as a conclusion he mentioned that

ovarian electrocautery for PCOS normalizes ovarian function, including androgen production (28).

Gonadotropin therapy is associated with an increased risk of multiple pregnancies and ovarian hyperstimulation (27). Gonadotropin contains follicle stimulation hormone (FSH), luteinizing hormone (LH) or both. As these hormones play a central role in egg production, a PCOS patient who is not ovulating early in the menstrual cycle, can have daily gonadotropin injections. If this results in mature follicles, the ovary is ready to ovulate (26).

In vitro fertilization (IVF) is reserved for PCOS women with unsuccessful gonadotropin therapy. This is a therapy where an egg is fertilized by sperm outside the body, and then is the fertilized egg reinserted into the uterus.

PCOS patients - mature women:

In mature women with PCOS, the treatment has to reduce long term complications such as diabetes mellitus type 2, metabolic syndrome and cardiovascular diseases. Diet and exercise are considered as first line treatment, especially in mature women.

Metformin, an oral anti hyperglycemic drug, is considered as a treatment in patients with type 2 diabetes mellitus. It is also considered in patients with PCOS who are insulin resistant. The American College of Obstetricians and Gynecologists recommends a fasting glucose level and a two hour glucose level after a 75 g glucose load as a screening for type 2 diabetes in women with PCOS (18). Around 7, 5% of women with PCOS have type 2 diabetes mellitus according to WHO based on an oral glucose tolerance test (15). Clinically, it has been shown that metformin effectively decreases androgen levels, as well as improving insulin sensitivity and facilitates weight loss in patients with PCOS as early as adolescents (29, 30). The main function of metformin is to reduce the level of insulin. Metformin also

affects the proliferation of theca cells and endometrial growth, inhibits the ovarian gluconeogenesis and contributes to reduced androgen production (26).

Metabolic syndrome in women is characterized by abdominal obesity with waist circumference >35 inch, dyslipidemia with triglyceride level >150 mg/dL, high density lipoprotein cholesterol level <50 mg/dL and elevated blood pressure (1). This syndrome will lead to increased risk of coronary artery calcification and atherosclerosis. Some patients with PCOS have to be treated with statins to reduce the risk of cardiovascular diseases. High blood pressure has to be treated with antihypertensives, if loosing weight, regular exercise and eating healthy does not help reducing it.

Overview of treatment options in PCOS patients.

Adolescents:	Infertile women:	Mature women:
<ul style="list-style-type: none">- Diet and weight regulation- Oral contraceptives. With acne: add anti-androgen- Laser or electrolysis for hirsutism	<ul style="list-style-type: none">- Diet and weight regulation- Clomiphene citrate- Gonadotropins or laparoscopic drilling- In vitro fertilization	<ul style="list-style-type: none">- Diet and weight regulation- Metformin- Antihypertensives and/or statins

5. Conclusion

There are many various definitions of polycystic ovary syndrome, but in most cases they include irregularities in the menstrual cycle, anovulation, hyperandrogenism, hirsutism and acne (14). The Endocrine Society released practice guidelines in 2013 using the Rotterdam criteria for diagnosing PCOS with the presence of two of the following: androgen excess, ovulatory dysfunction or polycystic ovaries (9). The exact pathogenesis in PCOS is unknown, even though there are many studies that conclude that hyperinsulinemia does play a major role (11).

Lifestyle modifications have a positive impact on the risk reduction for diabetes, as well as in restoring ovulatory cycles, improved hyperandrogenic features and in achieving pregnancy in women with PCOS (18). Diet regulation and weight loss are considered as a first line treatment.

As it is a complex syndrome and there is a variety in symptoms and signs in individuals with PCOS, the treatment must be adapted according to the individual's age, weight and insulin resistance. It should be considered as a goal, reducing the signs and symptoms of hyperandrogenism, insulin resistance and to recreate a normal menstrual cycle and ovulation with drug treatment in PCOS patients.

It is also necessary for those who are treating patients with PCOS to inform them about long term complications associated with this syndrome, such as infertility, diabetes, metabolic syndrome and cardiovascular diseases.

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